ABSTRACT

We describe here an *in vitro* method of increasing complementarity in a heteroduplex polynucleotide sequence. The method uses annealing of opposite strands to form a polynucleotide duplex with mismatches. The heteroduplex polynucleotide is combined with an effective amount of enzymes having strand cleavage activity, 3′ to 5′ exonuclease activity, and polymerase activity, and allowing sufficient time for the percentage of complementarity to be increased within the heteroduplex. Not all heteroduplex polynucleotides will necessarily have all mismatches resolved to complementarity. The resulting polynucleotide is optionally ligated. Several variant polynucleotides result. At sites where either of the opposite strands has templated recoding in the other strand, the resulting percent complementarity of the heteroduplex polynucleotide sequence is increased. The parent polynucleotides need not be cleaved into fragments prior to annealing heterologous strands. Therefore, no reassembly is required.